2. SYNOPSIS

Name of Sponsor/Company: The Medicines Company **Name of Finished Product:** Oritavancin **Name of Active Ingredient:** Oritavancin diphosphate	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study: A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin vs IV Vancomycin for the Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections (SOLO I)

Principal Investigator: G. Ralph Corey, MD

Investigators: 48 investigators

Study center(s): 46 study centers in the following countries: Germany (1), India (9), Israel (3), Mexico (2), Romania (2), Russia (2), Spain (1), Ukraine (3), United States (23)

Publications (reference): Manuscript in preparation

Study period: 9 weeks **Date first patient enrolled:** January 12, 2011 **Date last patient completed:** November 30, 2012	**Phase of development:** 3

Objectives:

Primary:

- To establish noninferiority of single-dose IV oritavancin compared with IV vancomycin given for 7 to 10 days using the primary efficacy outcome defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at the Early Clinical Evaluation (ECE) timepoint of 48 to 72 hours in the modified intent-to-treat (mITT) population

Secondary:

- To evaluate the clinical response ('clinical cure') associated with single dose IV oritavancin compared with IV vancomycin for 7 to 10 days at the End of Therapy (EOT) timepoint and sustained to Day 10 and the post therapy evaluation (PTE) timepoint in the mITT population
- To evaluate the clinical response for the primary efficacy outcome in the clinically evaluable (CE) population
- To evaluate the clinical response (clinical cure) of treatment with single dose IV oritavancin compared with IV vancomycin for 7 to 10 days at the EOT visit and sustained to Day 10 and the PTE visit in the CE population
- To evaluate the efficacy of single dose IV oritavancin in terms of clinical response (cessation of spread or reduction in size of the baseline lesion, absence of fever, no rescue antibiotic medication, and clinical cure) endpoints by pathogen, compared with vancomycin treatment in the microbiologically intent-to-treat (MicroITT) and microbiologically evaluable (MicroE) populations
- To evaluate the microbiological response, overall and by pathogen, of oritavancin compared with vancomycin treatment in the MicroITT and MicroE populations
- To evaluate the incidence of microbiological relapse or recurrence rates at the PTE visit in the MicroITT and MicroE populations
- To evaluate the clinical response (clinical cure) and microbiological response in patients in the CE and MicroITT populations meeting systemic inflammatory response syndrome criteria at Screening (defined as two of the following: temperature > 38°C, pulse > 90 beats per minute, respiratory rate

> 20 breaths per minute, white blood cell count > 12,000 cells/µL or < 4,000 cells/µL or > 10% bandemia), or with positive blood cultures

- To compare the safety and tolerability of a single IV dose of oritavancin with vancomycin IV dosed for 7 to 10 days
- To examine population pharmacokinetics (PK) and PK/pharmacodynamics (PD) of the oritavancin 1200 mg dose in the PK population

Additional objectives:

- To evaluate the ability of a single dose of oritavancin to resolve fever (≤ 37.7°C) at ECE (48 to 72 hours) compared with IV vancomycin for 7 to 10 days in patients presenting with fever (≥ 38°C) at baseline
- To characterize genes in strains of *Staphylococcus aureus* (*S. aureus*) and their association with clinical response and microbiological response in the MicroITT population
- To collect patient-level and hospital-level data to conduct a health economic evaluation of patients in each treatment group

Methodology:

This was a global, randomized, double-blind, parallel-group, Phase 3 clinical trial in patients with an acute bacterial skin and skin structure infection (ABSSSI) suspected or confirmed to be caused by a Gram-positive pathogen. Randomization was stratified by geographic region, study site, and diabetes mellitus diagnosis. An enrollment cap of 30% was maintained for major cutaneous abscesses. Lesion size was confirmed by photographs and planimetry.

Number of patients (planned and analyzed): Approximately 960 patients were planned to be randomized, including 70% (672 patients) clinically evaluable with at least 175 patients with methicillin-resistant *S. aureus* (MRSA). A total of 968 patients were randomized in the study; 954 were treated and 204 were infected with MRSA. A total of 954 patients were analyzed in the mITT population, 791 in the CE population, 204 in the MRSA MicroITT population, and 168 in the MRSA MicroE population.

Diagnosis and main criteria for inclusion: The study included patients at least 18 years old with an ABSSSI with a minimum surface area of 75.0 cm^2, suspected or known to be caused by a Gram-positive pathogen requiring at least 7 days of IV therapy. ABSSSI included traumatic and surgical wound infections (onset within 7 days prior to randomization and no later than 30 days following the trauma or surgical procedure); cellulitis/erysipelas (onset within 7 days prior to randomization); and major cutaneous abscesses. Inclusion also required the presence of signs and symptoms of systemic inflammation.

Test product, dose and mode of administration, batch number:

Oritavancin diphosphate (oritavancin) 1200 mg in mannitol, IV

On Day 1, patients randomized to oritavancin/placebo were administered Dose 1, a single 1200 mg IV infusion of oritavancin in 1000 mL 5% dextrose in water (D5W) given over 3 hours. Beginning with Dose 2, placebo infusions were administered to maintain the study blind relative to the active vancomycin treatment group. Starting with Dose 2 and for all subsequent doses of placebo, infusion time was a minimum of 60 minutes. Dosing was every 12 hours.

The lots of oritavancin used in this study were lot 2042806 and lot 2108927.

Duration of treatment:

Oritavancin: Single dose followed by placebo infusions every 12 hours for 7 to 10 days.

Vancomycin: Twice daily administration for 7 to 10 days

Reference therapy, dose and mode of administration, batch number:

Vancomycin hydrochloride, USP (vancomycin) IV

Vancomycin was administered for 7 to 10 days. On Day 1, vancomycin was administered as either a 1 g dose or at 15 mg/kg every 12 hours. After Day 1, the vancomycin dose could be adjusted by the unblinded pharmacist/designee based upon creatinine clearance levels, the patient's clinical status, and/or vancomycin trough levels. Vancomycin trough plasma concentrations were determined and the dose adjusted according to the local standard of care. The first dose of vancomycin on Day 1 was administered in 1000 mL D5W and

infused over 3 hours to maintain study blinding. Starting with Dose 2 and for all subsequent doses, infusion time was a minimum of 60 minutes.

The lots of vancomycin used in this study were lot 02275DD, lot 040513A, lot 153603A, lot 82400DD, lot W046916AA, and lot Y166923BA.

Criteria for evaluation:

Efficacy

Primary Outcome:

- Early clinical response defined as cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibiotic medication at ECE (48 to 72 hours). The definition of the primary endpoint meets the criteria recommended by the United States Food and Drug Administration (FDA) for the primary efficacy endpoint in ABSSSI studies [FDA, 2010].

Secondary Outcomes:

Key Secondary Efficacy Outcome

- Investigator-assessed clinical cure at the PTE visit in the mITT population. This is the key secondary efficacy endpoint specified in the Statistical Analysis Plan and is the primary endpoint for Europe as recommended by the European Medicine's Agency (EMA) [EMA, 2012].

Main Secondary Efficacy Outcomes

- Lesion area decrease ≥ 20% from baseline at ECE. This is a main secondary efficacy endpoint because it is the endpoint currently recommended by FDA and the Foundation for the National Institutes of Health [Talbot et al, 2012] as the primary efficacy endpoint for an ABSSSI treatment.
- Sustained clinical response at PTE performed using the mITT population. This is a main secondary efficacy endpoint because it demonstrates the clinical cure at EOT is sustained over time.

Supportive Secondary Efficacy Outcomes

- Investigator-assessed clinical response at EOT and Day 10 using the mITT population
- Sustained lesion area decrease at EOT and PTE using the mITT and CE populations
- Pathogen-level microbiological response at EOT, Day 10, and PTE
- Patient-level microbiological relapse at PTE visit
- Change from baseline in temperature and resolution (absence) of fever (temperature < 37.7°C), at ECE for patients presenting with fever (temperature ≥ 38°C) at baseline
- Rescue medication use
- Unplanned surgical procedures
- Signs and symptoms related to the primary ABSSSI site
- Change in patient's assessment of pain at the primary ABSSSI site

Safety Outcomes:

- Safety endpoints included adverse events (AEs), serious AEs (SAEs), all-cause mortality, premature withdrawals because of AEs, AEs of special interest, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, and electrocardiograms (ECGs)

PK Outcomes (conducted in a subset of patients)**:**

- PK parameters including area under the plasma concentration-time curve (AUC), half -life ($t_{1/2}$), clearance (CL), maximum concentration (C_{max}), and steady state volume of distribution (V_{ss})

Additional Outcomes:

- Association of the genotype in strains of *S. aureus* with clinical response and microbiological response in patients
- Evaluation and comparison of health economic parameters and resource utilization for patients with oritavancin or vancomycin

Statistical methods:

The primary analysis of early clinical response was performed using the mITT population. For the primary efficacy endpoint, 2-sided 95% confidence intervals (CIs) for the difference in rates of response between the two treatment groups were calculated (oritavancin rate minus vancomycin rate). Noninferiority of oritavancin was declared at the 1−sided alpha level of 0.025 if the lower bound of the 2-sided 95% CI was more than −10%. If noninferiority of oritavancin was declared, superiority was tested using the same 2-sided 95% CI and a lower limit of 0%. Supportive analyses were conducted using the ITT and CE populations. Sensitivity analyses were conducted: (1) excluding missing data and (2) treating missing data as treatment success.

The key secondary efficacy endpoint of investigator-assessed clinical cure rates at PTE and the main secondary efficacy endpoints of lesion-size reduction ≥ 20% at ECE and sustained clinical response at PTE were analyzed using the mITT population as for the primary efficacy endpoint. Investigator-assessed clinical cure rates at PTE and lesion-size reduction ≥ 20% at ECE were prespecified for noninferiority testing whereas sustained clinical response was not prespecified for noninferiority testing.

Descriptive analyses were performed for safety parameters by treatment group using the Safety population, defined as all patients who were dosed with study drug using the actual treatment received.

EFFICACY RESULTS:

As shown in the table below, the prespecified noninferiority margin for the primary and secondary efficacy endpoints were met.

Efficacy Results in the mITT Population

	Oritavancin % (Proportion)	Vancomycin % (Proportion)	Difference (95% CI)
Early clinical response	82.3% (391/475)	78.9% (378/479)	3.4 (-1.6, 8.4)
Investigator-assessed clinical cure at PTE	79.6% (378/475)	80.0% (383/479)	-0.4 (-5.5, 4.7)
Lesion size reduction ≥ 20% at ECE	86.9% (413/475)	82.9% (397/479)	4.1 (-0.5, 8.6)
Sustained clinical response at PTE	65.9% (313/475)	67.2% (322/479)	-1.3 (-7.3, 4.7)

Source: Tables 4.1.1.1, 4.2.1.1, 4.2.9.1, 4.2.15.1

Results for each efficacy endpoint were confirmed using the CE population.

A pathogen was isolated from 61.1% of patients in the oritavancin group and 61.0% of patients in the vancomycin group at baseline; most of these patients had a Gram-positive pathogen known to cause ABSSSI (oritavancin, 96.2%; vancomycin, 95.5%). *S. aureus* was the most common pathogen (oritavancin, 78.1%; vancomycin, 75.8%) and MRSA was recovered from the primary ABSSSI site or blood culture in 104 patients treated with oritavancin and 100 patients treated with vancomycin. As shown in the table below, efficacy was confirmed in patients with MRSA.

Efficacy Results in MRSA Subgroup (MicroITT Population)

	Oritavancin % (Proportion)	Vancomycin % (Proportion)	Difference (95% CI)
Early clinical response	80.8% (84/104)	80.0% (80/100)	0.8 (-10.1, 11.7)
Investigator-assessed clinical cure at PTE	82.7% (86/104)	83% (83/100)	-0.3 (-10.7, 10)
Lesion size reduction ≥ 20% at ECE	90.4% (94/104)	84% (84/100)	6.4 (-2.8, 15.5)
Sustained clinical response at PTE	70.2% (73/104)	71% (71/100)	-0.8 (-13.3, 11.7)

Source: Tables 4.1.6.3, 4.2.6.3, 4.2.13.3, and 4.2.20.4

PK RESULTS:

PK samples were collected from 115 patients treated with oritavancin. The mean plasma concentration at 3 hours on Day 1 (approximately 15 to 30 minutes after the end of first infusion) was 119.3 µg/mL (standard deviation [SD] 45.55 µg/mL). The mean plasma concentration of oritavancin declined at each subsequent time point to 0.9 µg/mL (SD 0.30 µg/mL) at 576 hours (Day 24). Vancomycin trough plasma concentrations (prior to the fourth dose) were available for 433 patients; the mean trough level was 15.38 µg/mL (SD 30.395 µg/mL).

SAFETY RESULTS:

This study demonstrated that a single 1200 mg IV dose of oritavancin was well tolerated and had a similar safety profile to 7 to 10 days of vancomycin treatment (1 g or 15 mg/kg twice daily) (see table below).

Overall Summary of Adverse Events (Safety Population)

Category	Oritavancin (N = 473) n (%)	Vancomycin (N = 481) n (%)	All Patients (N = 954) n (%)
Patients with any AE	284 (60.0)	307 (63.8)	591 (61.9)
Study drug-related AE[a]	108 (22.8)	151 (31.4)	259 (27.1)
AE leading to study drug discontinuation	18 (3.8)	28 (5.8)	46 (4.8)
SAE	35 (7.4)	35 (7.3)	70 (7.3)
AE leading to fatal outcome	1 (0.2)	2 (0.4)	3 (0.3)

[a]Includes AEs considered by the investigators as definitely related or possibly related to study drug.
Source: Table 6.1.5.

The most common AEs (≥ 2%) in the oritavancin vs vancomycin group were nausea (11.0% vs 8.9%), headache (7.2% vs 7.9%), vomiting (4.9% vs 3.7%), diarrhea (4.9% vs 3.5%), cellulitis (4.2% vs 3.5%), infusion site reaction (4.0% vs 7.1%), and constipation (4.0% vs 4.4%). The majority of AEs in both treatment groups were mild.

The frequency and distribution of SAEs was similar in both groups (oritavancin, 7.4%; vancomycin, 7.3%). The most common SAE was cellulitus (oritvancin, 5 patients [1.1%]; vancomycin, 8 patients [1.7%]).

Three patients, one in the oritavancin group and two in the vancomycin group, died during the study. The patient in the oritavancin group died from sepsis which was assessed by the investigator as unrelated to study drug. In the vancomycin group, one patient died of septic shock and one patient died of advanced dementia with Parkinsonism; both of these events were assessed by the investigator as unrelated to study drug.

There was no difference between the oritavancin and vancomycin groups in any of the AEs of special interest.

The incidence of laboratory abnormalities, including liver and renal function test results, was similar between the groups. No difference in vital signs and ECG findings were identified between groups.

CONCLUSION

The study established noninferiority of single-dose IV oritavancin compared with IV vancomycin given twice daily for 7 to 10 days as assessed by: 1) the primary efficacy endpoint of early clinical response at 48 to 72 hours, using criteria recommended by FDA [FDA, 2010] and 2) investigator-assessed clinical cure at PTE using criteria recommended by the EMA [EMA, 2012]. Single-dose IV oritavancin was therefore effective in treating ABSSI and well tolerated with a safety profile at least as favorable as IV vancomycin.

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